original research report

Immunohematopoietic stem cell transplantation in Cape Town: a ten-year outcome analysis in adults

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Hematol Oncol Stem Cel Ther 2009; 2(2): 320-332

BACKGROUND AND OBJECTIVES: Immunohematopoietic stem cell transplantation has curative potential in selected hematologic disorders. Stem cell transplantation was introduced into South Africa in 1970 as a structured experimental and clinical program. In this report, we summarize the demography and outcome by disease category, gender, and type of procedure in patients older than 18 years of age who were seen from April 1995 to December 2002.

PATIENTS AND METHODS: This retrospective analysis included 247 individuals over 18 years of age for whom complete data were available. These patients received grafts mostly from peripheral blood with the appropriate stem cell population recovered by apheresis.

RESULTS: Patient ages ranged from 20 to 65 years with a median age of 42 years. There were 101 females and 146 males. There were no withdrawals and 63% survived to the end of the study. At 96 months of follow-up, a stable plateau was reached for each disease category. Median survival was 3.3 years (n=6, 14.6%) for acute lymphoblastic anemia, 3.1 years (n=44, 18%) for acute myeloid leukemia, 2.8 years (n=47, 19%) for chronic granulocytic leukemia, 2.8 years (n=71, 29%) for lymphoma, 1.5 years (n=23, 9%) for myeloma, 1.43 years (n=10, 4%) for aplasia, and 1.4 years (n=38, 15%) for a miscellaneous group comprising less than 10 examples each. Multivariate analysis showed that only diagnosis and age had a significant impact on survival, but these two variables might be interrelated. There was no significant difference in outcome by source of graft.

CONCLUSION: The results confirm that procedures carried out in a properly constituted and dedicated unit, which meets established criteria and strictly observes treatment protocols, generate results comparable to those in a First World referral center. Low rates of transplant-related mortality, rejection and graft-versus-host disease are confirmed, but the benefits cannot be extrapolated outside of academically oriented and supervised facilities.

Traditional allogeneic bone marrow transplantation, introduced primarily for correction of irreversible aplasia whether congenital[1] or acquired[2] may also be life saving in other defects exemplified by immunodeficiency disorders[3] and metabolic diseases.[4] It is currently accepted as having a place in treating acute[5] and chronic leukemia,[6] Hodgkin[7] or indolent[8] as well as aggressive lymphoma[9] in addition to myeloma.[10] The scope increasingly extends to a number of solid tumours amongst which are breast cancer[11] and, in selected cases, acquired lesions including paroxysmal nocturnal haemoglobinuria[12] or myeloproliferative syndromes amongst which is idiopathic myelofibrosis.[13]

Outcome continues to benefit from more precise matching at both major[14] and minor[15] histocompatibility loci, using DNA-based or molecular techniques, which also make possible definition of chimerism16 or quantitation of minimal residual disease.[17] Nevertheless problems persist amongst which are rejection[18] and acute[19] or chronic graft-versus-host disease.[20] These are offset by better utilisation of immunosuppressive regimens for conditioning[21] as well as in the post-procedure period with corticosteroids, methotrexate,[22] cyclosporin,[23] tacrolimus[24] and mycophenolate mofetil.[25] Concurrently

there is greater attention being given to supportive care,[26] proactive evaluation and maintenance of nutrition underpinned by strong psychosocial networks.[27]

Against such a background this therapeutic option was introduced into South Africa in 1970 via an animal allograft program[28,29] with active research and ongoing clinical development sustained by the original internationally designated team. On this basis it has been possible to provide a forty-year perspective in which four separate developmental, albeit overlapping, periods can be identified with the appreciation that such distinction is somewhat artificial.[30]

Firstly was a need to pioneer the use of apheresis in this country so replacing the obsolete delivery of blood products in bottles and, applied initially, to explore a place for granulocyte transfusions.[31] There was subsequent permeation of the technology into commercial blood banks where, in the course of the last 30 years, it has entirely appropriately become a well-established routine. Concomitantly to expand the use in processing bone marrow after collection whilst, latterly, to directly harvest the corresponding population after mobilisation with stimulatory peptides into the peripheral blood.[32] The latter resulted in a substantially shortened time to engraftment,[33] a low incidence of relapse in acute myeloid leukemia, but reappearance of cytomegaloviral infections.[34]

Secondly were preliminary cooperative studies with Jeanne Borel at Sandoz in Basle showing that cyclosporin A, at least in experimental animals, decreased both the incidence and severity of acute graft-versus-host disease. Follow-up in the clinic, however, revealed that while these benefits could be reproduced in patients, prevention was only partial and did not abrogate recurrence.[35]

Thirdly there followed collaborative research initially in Cambridge[36] and with the same group continuing these investigations latterly in Oxford[37] that defined a role for T-lymphocyte depletion using Campath monoclonal antibodies in vitro by adding them to the graft in-the-bag.[38] One consequence was recognition of an altered expression or forme fruste of immunologically mediated acute graft-versus-host disease that appeared later, was typically limited to skin and usually responsive to topical steroids although on occasions systemic administration was unavoidable.[39] This syndrome is not considered chronic in the accepted sense either to time of onset or more importantly having a quite different clinical spectrum and remains distinct being conceptually regarded as reflecting modulation by the antibody used in this particular way. Such an approach remains firmly established as local, and much wider, practice.[40] It also forms part of the broader ongoing participation and reporting of results to the Campath users group.[41] The original lytic IgM protein was subsequently replaced by an opsonic equivalent and more recently shift to a chimeric humanised version designated Campath 1H.[42] In all these studies engraftment remains uniform and rejection infrequent. This applies even when extended to include family members and matched unrelated volunteer donors identified through the South African Bone Marrow Registry[43] interacting with corresponding European Centers and the American National Donor Program[44].

Fourthly, appreciating that peer review was crucial to maintaining standards, but unfortunately non-existent in this country or anywhere in sub-Saharan Africa, every patient, from inception, has been reported to the International and then Autologous Bone Marrow Transplant Registries for scrutiny and audit. After more than twenty years of refinement and consolidation, our original program was transferred, in 1995, to an academic Department in the private sector. Maintenance of this active surveillance mechanism, now to the Center for International Blood and Bone Marrow Transplant Research, has sustained unbroken reaccreditation to the present time. Concurrently the original group remain designated as a Transplant, Harvest and Donor Center within European Bone Marrow Transplant Registry and concurrently with participation and approval for transplantation as well and as harvesting by the American National Donor Program.[44]

After 30 years it is appropriate that this single team experience be updated to allow comparison, particularly in the last decade, to other private and state services in this country, but, more critically, to be measured against results on a worldwide basis.

It is mandatory in South Africa, as in other emerging, developing or under-resourced areas, that a clear and reliable statement of what can be expected is available. Such statistically analysed data provides perspective against which to evaluate changes that continue to occur as a result of the ever-shifting stance of managed health care providers for insured patients. This is especially relevant as government starts to focus on costs in private hospitals whilst medical aids seek to define preferred providers, not as one would expect on cost-effective benefits, but primarily using financial or incentive - driven criteria. Scientifically, academically and intellectually, it is argued that such monetary focus is inappropriate and should defer to the identification of high-performing multidisciplinary units that can meet the requirements for the widely acknowledged center effects.[45,46] Corresponding information for those under 18 years of age is the subject of a separate publication.[47] To definitely document the introduction and subse-

quent development the comprehensive experience in this country has recently been reviewed.[48]

Also the wider place of these interventions from introduction at the University of Cape Town and Groote Schuur Hospital in 1970 with establishment in the private sector with continued development over the last 15 years is in preparation for the History of Medicine Series.[49]

Accordingly, we detail, from this academic unit in Cape Town, statistically analysed results and define projected basic as well as clinical research that will focus on immunologic reconstitution.[50] The latter is anticipated to correlate laboratory findings with patient response to viral, parasitic and bacterial infections in the context of reverse isolation and emerging multi-drug resistance.[51] The particular relevance is that this program will explore immunosuppression by only ex vivo T-cell depletion that is distinctly different from many more conventional approaches where a range of agents are administered for periods of time after engraftment for control of rejection and graft versus host disease. Additionally, to better document commitment to quality-of-life assessment with psychosocial counselling in conjunction with liaison psychiatry. There already emerges a strong argument to restrict these costly treatments to active teams that have a clear record of meeting first world performance judged by published outcome, attract sufficient volume to sustain the advantages of the well-recognised center-effect[52,53] and, in developing or under-resourced areas, meet criteria for international acceptance via endorsement as full participating membership in appropriate registries.[54] Indeed it has recently been proposed that these activities be collected and analysed by establishing a repository within the South African Bone Marrow Registry to match the ongoing survey by European Bone Marrow Transplant Group.[55] The latter focuses on cord blood but draws attention to the widely recognised argument to require reporting of all procedures whilst leaving the way open for local groups to assign resources regionally. These are not exclusive but can readily be revised to include survival analysis in the future.

PATIENTS

Three hundred and twenty Consecutive individuals, over 18 years of age, eligible for immunohaematopoietic stem cell transplantation were registered from April 1995 to December 2002, a number of which were included in a recent audit by the Center for International Blood and Marrow Transplant Research and retrospectively analysed. After the data was cleaned to implement age restriction a total of 247 cases qualified as the basis for this report.

METHODS

Diagnosis

Following comprehensive clinical assessment agreed definitions were used for aplasia,[1] acute[5] and chronic[6] leukemia, Hodgkin[7] or other lymphomas[9] and myeloma.[10] Morphologic features on bone marrow aspiration were supplemented by appropriate cytochemistry,[56] flow cytometry,[57] karyotyping and molecular genetics documented.[58] Immunohistochemistry was used as necessary on tissue and trephine biopsies.[59]

Radiology

Conventional films were complemented by computerized axial tomography including determination of bone mineral density.[60] Skeletal involvement was recorded and changes graded according to locally developed criteria (unpublished). The preferred PET-CT was not routinely available during this time.

Biochemistry

Renal and hepatic profiles, serum protein electrophoresis, immunoglobulin quantitation and markers of tumour activity included sensitive C-reactive protein and ß2 microglobulin.

Staging

Where relevant this was according to the Cotswold modification of the Rye system or, preferably, the international prognostic index.[61]

Pre-transplant phase

Physical facility

Management was in reverse isolation where each two-roomed suite had dedicated shower and toilet. There was a particular focus on patient information and interactive counselling offered to help maintain optimum quality of life.[62-64] In addition details of local bone marrow transplant unit was provided in two specially written information brochures.[65,66]

Nutritional status

Selective decontamination of the bowel relied on oral levofloxacin.[67] A low microbial diet was provided with daily review of weight, caloric status and vitamin as well as trace metal balance.[68] All patients were in the routine care of a trained academic dietician.

Where targets were not achieved placement of a nasojejunal, as opposed to nasogastric, fine bore feeding tubing was used and this remains a subject of evaluation (Wood, Schloss, O'Keefe, Jacobs - study in progress).

Total parenteral nutrition was infrequently needed and then largely in the paediatric age group.

Nausea and vomiting

These symptoms were anticipated and recipients received 72 hours of oral phenobarbitone, metoclopramide or serotonin antagonists prior to admission. This was switched to intravenous route at the time of conditioning and dosage titrated to proactively prevent such side effects with this regimen supplemented by paracetamol, dexamethasone or valoid orally or by suppository as needed. More recently neurokinin-1 antagonists and second-generation 5-hydroxytryptamine antagonist[69,70] have become available and, together with motility-controlling drugs, were used when indicated.[71] Clostridium difficile was treated with oral metronidazole or, if resistant, vancomycin by the same route.[72]

Neutropenic fever and viral infections

Pyrexia, defined as 38°C, when confirmed at 60 minutes, required repeated cultures of blood, urine and stool followed by empiric single agent ceftazidime[73] or tazocin[74] with the beta-lactams given as 24-hour continuous intravenous infusion. Isolation of pathogens was the basis of switching to in vitro sensitivity directed regimens and typically with 2 drugs synergistic in vitro for persisting fever.

Culture-negative cases were managed with 1 mg/kg of amphotericin in 200 ml 5% dextrose water given, as a continuous 24-hour infusion since side effects, and particularly nephrotoxicity, were abrogated.[75]

Cytomegalovirus was monitored by serology and more recently routinely screened for by the PP65 and PP67 assay with polymerase chain reaction when leukocyte counts were below 1×10^9/L. Pre-emptive treatment was by intravenous gancyclovir[76] or valganciclovir[77] and switched to the latter agent orally for a further two weeks once the virus was no longer detectable. It is notable that, at least in solid organ transplants related to the pharmacokinetics[78] and pharmacodynamics,[79] both agents can result in drop in white count and delay recovery in neutrophil and monocyte levels.[80,81]

Transfusion policy

Neutropenia, particularly when associated with fever, of less than 0.5×10^9/L granulocytes received 300g GCSF intravenously until this level was stable above 1×10^9/L and temperature again normal.[82,83] Packed red cells were administered on a standard regimen for symptom-relief with haemoglobin arbitrarily kept above 100 g/L.[84] Platelets were used in those at risk from bleeding to maintain counts greater than 30×10^9/L with single-donor apheresis units[85,86] concurrently with 500 mg of cyklokapron orally or intravenously every 8 hours.[87] These were collected initially from a dedicated volunteer panel[88] and with quality control to meet safety standards.[89]

Surveillance

Data analysis was on a moment-to-moment basis. All decisions were updated daily at morning report and included planning for nutrition, psychosocial counselling, liaison psychiatry, physiotherapy with review of medication by haematology pharmacists.

Central venous access

This was secured using a double-lumen Brovic catheter inserted under general anaesthetic following the Hickman technique.[90] The position was checked on recovery to confirm that return of muscle tone did not dislocate the tip, ideally positioned 1 cm above the junction of the superior vena cava with the right atrium.[91] Low dose warfarin, with the INR in the normal range, was employed to reduce the risk of venous thromboembolism.[92]

Counselling and liaison psychiatry

At diagnosis a family conference was convened that included introduction to nursing and paramedical staff, dietician and physiotherapist. Previous cytotoxic drug treatment and irradiation was documented and the risks, as well as potential benefits, of the procedure explained and brochures describing the organisation of the department and the unit provided. Once all issues had been fully discussed the informed consent was signed by patient or, in the case of minors, by parents or responsible guardians.

Prior treatment protocols

Donor selection

Histocompatibility was confirmed by standard methods[93] via the South African Bone Marrow Registry[43] where appropriate searches extended to include British, Australian, Dutch and American participating centers: further consultation was with the Leiden Group. These activities were part of a worldwide research project with certification through the International Immunogenetics Group.[94]

Acute lymphoblastic leukemia (n=14: 6%)

Treatment was standardised to the Berlin-Frankfurt-Munster or BFM programs.[95,96]

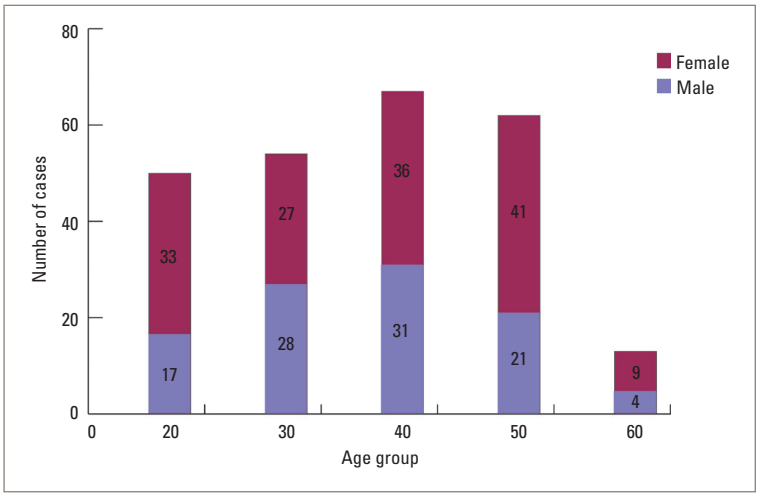

Figure 1. Demography by age and gender.

Acute myeloid leukemia (n=44: 18%)

Initially the combination of cytosine arabinoside, an anthracycline antibiotic with an epipodophyllotoxin[97,98] was used. More recently this was extended to the British Medical Research Council AML 15 program. In some instances managed health care organisations, on advice of their local consultants, have unfortunately restricted access to these regimens despite clear evidence of benefit from adding gemtuzumib ozogamicin to this drug regimen.[99]

Chronic granulocytic leukemia (n=47: 19%)

Disease control was rapidly achieved using hydroxyurea and latterly imatinib mesylate.[100] Transplantation was offered to fully matched recipients particularly with the escape from the tyrosine kinase, if cytogenetic abnormalities developed or this was patient's choice.[101]

Hodgkin and other lymphomas (n=71: 29%)

Current protocols parallel those used by the European Organization for Research and Treatment in Cancer[102,103] or the German Hodgkin and Lymphoma Study Group.[104,105]

Myeloma (n=23: 9%)

Stratification was by comorbidity[106] and risk factors using guidelines from the International Myeloma Working Group.[107] VECD comprising vincristine, epirubicin, cyclophosphamide and dexamethasone[108] were preferred. Here the target was greater than seventy-five percent reduction in both paraprotein level and plasma cell infiltrate of marrow trephine biopsy to qualify for autologous immunohaematopoietic stem cell grafting. Thalidomide was not approved by local Third Party funders during these studies. In appropriate cases maintenance depended on negotiating for this agent with bortezomib still not being available. Alternatives were pulsed melphalan and methylprednisolone or salvage with dexamethasone and vinorelbine.

Aplasia (n=10: 4%)

Intensive support included limiting blood and other components as far as possible. Where suitable sibling donors were available this remained the preferred treatment. In other instances immunosuppressive regimens including high dose methylprednisolone and antilymphocyte globulin were standard.[109-111]

In keeping with established practice, including this country, irreversible bone marrow failure was a prime indication for one or other form of immunohaematopoietic stem cell allografting either matched sibling, unrelated or minimally mismatched family donors.

Miscellaneous group (n=38: 15%)

This varied by subtype. In hairy cell leukemia 2-chlorodeoxyadenosine[112] was largely successful and so seldom needed grafting. Cutaneous lymphomas, including mycosis fungoides or Sezary syndrome, received appropriate superficial irradiation.[113,114] Gemcitabine[115] or alemtuzumab[116] for tumours of T-lineage and individualised therapy in B-lymphocyte neoplasms appropriate for risk category.[117] Individuals received pulsed chlorambucil or combinations of rituximab, fludarabine and cyclophosphamide: latterly the anti-CD52 monoclonal antibody Campath or alemtuzumab.[118] In selected refractory instances allografting was an option.[119]

Special projects

A number of prospective investigations are actively evaluating changes in pulmonary,[120,121] skeletal,[122,123] gastrointestinal,[124-126] renal[127] and cardiovascular status[128,129] as an integral part of management and incurred no new costs. Immunologic reconstitution[130,131] is to become a major focus of the program to explore the importance of side effects better now described as survivorship.[132,133]

Transplantation phase: conditioning regimens

Two myeloablative options were used. In none of these patients was this primarily immunosuppressive-alternatively described as reduced intensity.

Radiotherapy

12 gray fractionated whole body irradiation on days -7-6-5 is followed by 60 mg/kg of cyclophosphamide intravenously on days -4 and -3, and 6 gray fractionated total nodal irradiation on days -2 and -1. The graft is infused on day 0.

Chemotherapy

Busulphan combined with cyclophosphamide, used originally in the four-day regimen has been replaced by two-day alternative: the former being intravenous as opposed to oral.[134,135] In selected individuals, where this agent was contraindicated, fludarabine was used. Additionally in over eighty percent of our cases the first choice was the BEAM preparative regimen.[136]

Re-transplantation

With primary or secondary graft failure preparation was with fludarabine[137] antilymphocyte globulin and cyclophosphamide.[138]

Mobilization and quality control

Granulocyte-colony stimulating factor was commenced subcutaneously on Day 5 at a flat dose of 300µg with the last injection at 04h00 on the day of first large volume apheresis harvest. CD34 population were noted but not specifically used to time these collections.[32]

Autografts

Cyropreservation was undertaken as previously described.[139]

Allogeneic transplants

Histocompatible siblings received only the ex vivo T-cell depleted product after exposure to Campath 1H in-the-bag.[38] Alternative family members and matched unrelated volunteer donors - exclusively - received cyclosporin at full therapeutic dose for six months with a fifty percent reduction at three months and the remaining three months at twenty five percent optimum dose.

Infusion techniques

Premedication, given half an hour before the graft containing the monoclonal antibody, consisted of 100 mg of hydrocortisone, 12.5 mg of promethazine hydrochloride intravenously and 500 mg paracetamol orally. Continuing non-invasive cardiovascular and respiratory monitoring was sustained until vital signs were stable. Oxygen desaturation necessitated rate adjustment of this infusion and this occurred in less than five percent of the procedures. In approximately thirty percent pyrogenic reactions with abdominal discomfort were attributed to the immunoglobulin. There were no lasting side effects. In autografts transient fever was initially attributed to presence of DMSO and recently ascribed to contaminating granulocytes in the apheresis product.[140]

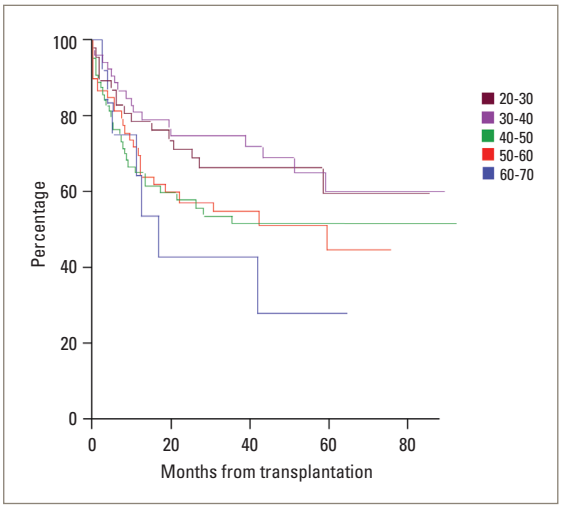

Figure 2. Survival by age.

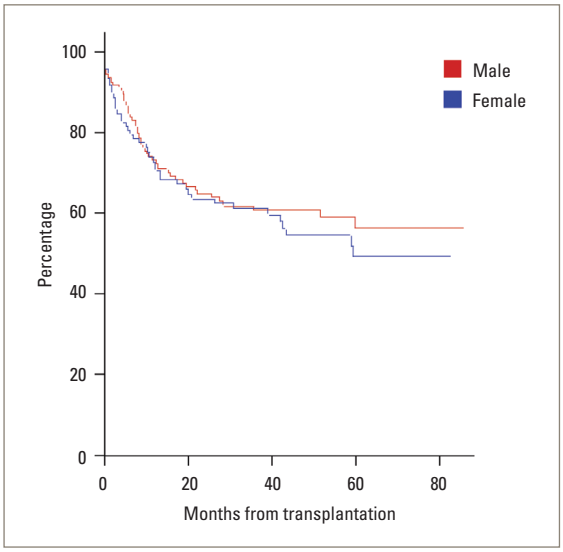

Figure 3. Survival by gender.

Product manipulation

Bone marrow, although no longer routinely used, continued to accommodate matched unrelated volunteer programs predicated on requirements of the collaborating center from different parts of the world. Here the harvest was modified using the standard apheresis technology: vide supra:[139] once greater than ninety-five percent of the mononuclear cells have been recovered the residual blood was reinfused to the donor or discarded. The immunohaematopoietic stem and progenitor concentrate had the standard ex vivo addition of 20 mg of Campath 1H, incubated at 37° for half an hour and infused.[38]

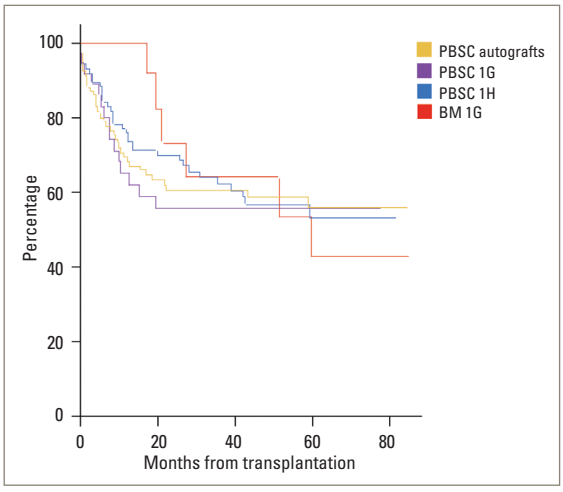

Figure 4. Impact of Compath antibody species.

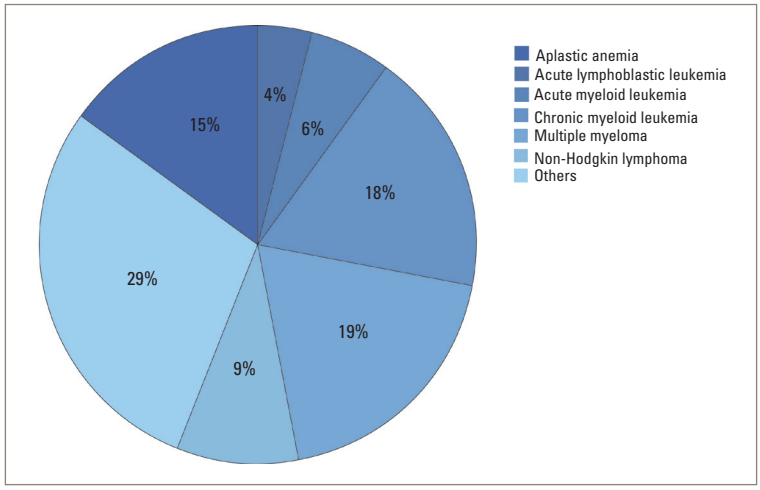

Figure 5. Disease distribution.

Peripheral blood collections required a minimum number of 6.5×10^8/kg mononuclears and preferably greater than 2×10^6/kg CD34 positive population. Long term colony initiating cells were determined in clonogenic assay.[141,142] It was noted that, whilst remaining standard, there is evidence that this particular approach may not optimally predict outcome especially in cord-derived grafts.[143] Specifically in only four patients who failed to meet this criteria there was, nevertheless, rapid reconstitution of normal values.

Pain management

This was according to World Health Organization guidelines.[144]

Post-transplant surveillance

Immunosuppression was not used in histocompatible siblings. Conversely, in family members and matched unrelated donors, the recipients received cyclosporin maintaining therapeutic levels of 1500 ng/mL on the C2 assay:[145] the dose was cut to fifty percent at six months, twenty five percent at nine months and discontinued at twelve months protocol included 200 mL of stabilised human serum weekly[146] in addition to 500 mg of valaciclovir twice daily for viral prophylaxis for three months and co-trimoxazole comprising trimethoprim 80 mg and co-trimoxazole 400 mg daily for one year.[147,148]

Statistical analysis

Data was examined using the Kaplan-Meier product limited estimator, Cox proportional hazard based on initially fitting each risk factor, multivariate analysis and Pearson Chi squared contingency tables for independence testing.[149,150]

RESULTS

Age and gender

Median and mean age were both 42 years with a range from 19.45 to 65.0 (Figure 1). At transplantation, mean age for females was 41.3 years and that for males 42.7 years. Most were between 40 and 50 years with a much-reduced number between 60 and 70. There were 101 female and 146 males. Gender was balanced in the middle but at the other end of the spectrum roughly double the number of males were present. Survival decreased with age (Figure 2) but despite difference between the groups, it is notable that the estimate of survival function is roughly the same. This suggests that once the initial transplant-related mortality is past, there is equal benefit from the procedure. There are no gender differences evident (Figure 3).

Influence of transplantation procedure

When subdivided by those having peripheral blood stem cell autologous or allogeneic transplants and further into groups were the graft source was from bone marrow or peripheral blood treated respectively with the of opsonic monoclonal antibody Campath IG or the humanised variant designated IH survival appears unaffected by the immunoglobulin (Figure 4). There was no statistical difference between control patients receiving peripheral blood stem cell autografts (n=101) when ex vivo t-cell depletion is carried out with the Compath IG bone marrow (n=14) or blood (n=36). Similarly, when humanized monoclonal antibody IH was used in-the-bag on the mononuclear

cells drived by apheresis from the circulation (n=96) outcome was comparable.

Outcome by diagnosis

The majority of the patients were referred with non-Hodgkin lymphoma followed by chronic granulocytic and then acute myeloid leukemia (Figure 5).

Analysis of survival on this basis (Figure 6) (Table 1) shows substantial differences with superiority for the acute leukemias followed by lymphoma although these are not stratified for Hodgkin and other variants with approximately equal outcome for the remaining cases with aplasia and myeloma.

Cause of death

The majority were multifactorial having a final common pathway of severe inflammatory response syndrome[151] culminating in multiple organ dysfunction.[152] Where separation and assignment to particular predominant explanation was possible, relapse, followed by respiratory failure accounted for most of the remainder with small numbers probably artificially attributed to septicaemia and cerebral events (Figure 7).

DISCUSSION

The introduction initially as conventional transplantation of bone marrow and subsequent development in South Africa over the ensuing 35 years[48] has, in the last decade, started to raise questions about sustainability of these often life saving, albeit costly, endeavours. Unquestionably they require a substantial investment of resources in providing tertiary or even quaternary level physical facilities originally based in state supported University teaching units but increasingly re-deployed at privately funded hospitals or clinics. Both areas depend for continued effective function on retaining a stable complement of highly trained and experienced doctors with nurses as well as paramedicals that make up the indispensable multidisciplinary team. Here arises the first problem, and it is as acute as serious, with severe understaffing becoming ever more critical at all levels reflecting a steadily accelerating exodus from South Africa of these professionals. Secondly, in monetary terms, there is inevitable competition with other health care priorities most strikingly in sub-Sahara by those created in the wake of an escalating acquired immunodeficiency disease pandemic.

Sharp focus is given to these sobering realities by an analysis describing such activities in Europe[153] coupled with a recent survey for the first time documenting the current local situation.[30] Accordingly the time was judged appropriate to set out the way in which the latter point had been reached[154] with a further intention of offering perspective for the future of immunohaematopoietic stem cell grafting in a Third World country seeking to objectively balance need against capacity. Such a repository has a number of potential benefits. It will allow government or other licensing authorities to look at the way regional activities are distributed. Secondly to ensure equitable accessibility to state funded programs and for all centers, particularly those in the private sector, to show effectiveness in adults and children, determined objectively by outcome analysis. Such impartiality facilitates scrutiny by managed healthcare organisations and medical aids of results from individual teams and so shifts the responsibil-

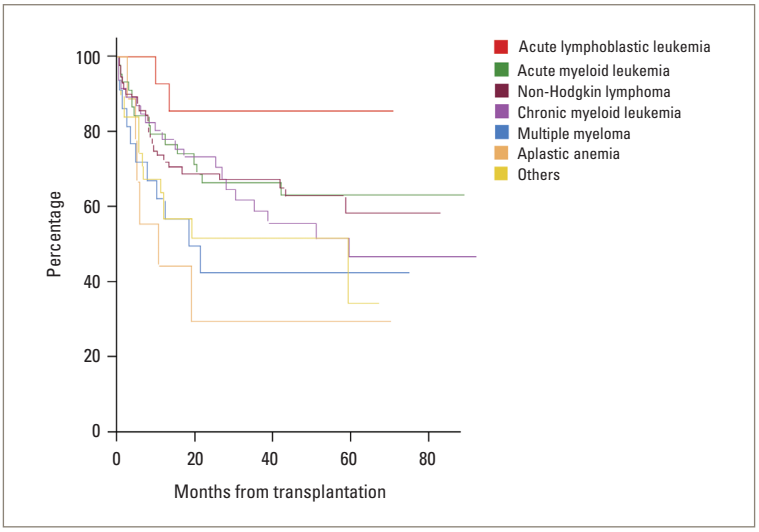

Figure 6. Outcome by diagnosis.

Table 1. Survival time in years from diagnosis.

Diagnosis	Number	Mean	Median	Minimum	Maximum
Acute myeloid leukemia	44	3.131	3.436	0.025	7.496
Acute lymphoplastic leukemia	14	3.301	2.929	0.814	5.923
Chronic myeloid leukemia	47	2.81	2.334	0.019	7.726
Lymphoma	71	2.764	3.142	0.011	6.94
Multiple myeloma	23	1.543	1.025	0	6.307
Aplastic anemia	10	1.433	0.697	0.074	5.885
Others	38	1.394	0.781	0.014	5.66

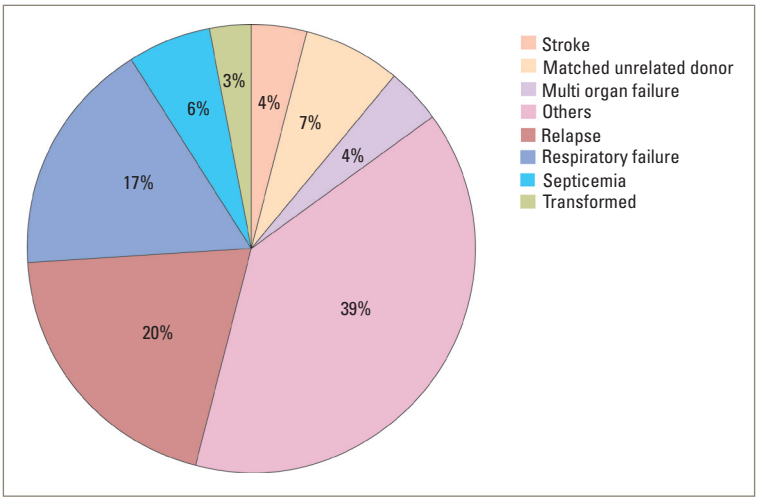

Figure 7. Causes of death.

ity to ensuring that potentially incentive-driven financing is replaced by supporting preferred providers where audit and accountability take into consideration the all-important center effect.

In an endeavour to provide this type of non-partisan information consecutive admissions over a seven-year period were analysed from an academic center based in the private sector. The facility was specifically created to recapitulate the standard University style department. Interestingly the same investigators that designed and commissioned the prototype and custom-built bone marrow transplant unit in the Groote Schuur Hospital have extended this experience over 35 years.[48]

Thus with the relocation of the Jean Porter apheresis unit and many of the professional nurses it has been possible to continue reporting consecutive recipients to the Center for International Bone Marrow Transplantation Research. This has ensured that their scheduled audits continue with accreditation: a status, which has remained intact for more than three decades.

Using this database the paediatric results could be compared to earlier experience from the State Hospital and document, apart from a more active private program, essentially the same results.[47]

The parallel experience in our adult cohort supports five conclusions.

Firstly, given a suitable physical facility and adherence to management protocols that are commensurate with international standards of care, an environment could be created to meet and then sustain established criteria for international standard of care whilst continuing to develop and introduce new research topics as appropriate. The cardinal consideration was a focus on the all-important haematology co-ordinator managing a multidisciplinary management team made up of long stay nursing and paramedical professionals including academic dieticians and skilled janitorial support staff with constant interaction between infectious disease, cardiology, nephrology and gastroeinterology consultants. Such a comprehensive unit emerges as the indispensable key to provision of unquestionably costly, albeit sophisticated, interventions with the all-important appreciation that this is an entirely realistic undertaking even in an under-resourced area of the globe.

Secondly, under these circumstances, outcome analysis is seen to approximate that from recognized reference centers in the field. This applies in the first three months with mortality largely related to the procedure itself. Then also, and of note, given the vagaries of southern Africa with migrant populations and civil unrest, the opportunity of serially observing these individuals for more than 35 years to provide a reliable long term reference point for overall cost effectiveness.

Thirdly in the specific context of ex vivo T-cell depletion is the seminal observation that survival curves are stable and do not have late and previously unrecognised sequelae that differ from those generated in recipients exposed to conventionally used post - transplant immunosuppressive regimens. Thus there is no apparent impact of this unique immunosuppressive regimen on developing myelodysplasia or predisposing to chronic infections such as pulmonary tuberculosis so rampant in sub-Saharan Africa. It remains to be determined whether the slightly higher incidence of cytomegaloviral infections translates into any clinically important requirements other than the need for prompt recognition and proactive antiviral therapy. It is also momentarily unclear as to whether the impact of retroviral infections can be altered in the face of appropriate combination active retroviral therapy and this is the subject of ongoing study.[155] Currently the quality-of-life with the low incidence of graft versus host disease, in its various forms, is gratifying.

Fourthly veno-occlusive disease has not been seen despite the use of intravenous busulphan. Furthermore peripheral blood stem cell mobilisation with G-CSF has been efficient with only relatively minor side effects of backache and bone pain in some donors. No difference can be seen when bone marrow is compared to peripheral blood as source of the graft. Also, and of relevance, is that no serious adverse reactions[156] have thus far been noted in donors despite which informed consent has been altered to include extended surveillance both among siblings and matched unrelated volunteers

through each referring registry.[43,157]

Fifthly, immunohaematopoietic stem cell grafting including collaboration on a worldwide basis is entirely realistic in this country given that donations can be imported or exported with due observance to rules on moving human tissue between countries.[43,158] This, in turn, is relevant and underlines the importance of our having established the South African Bone Marrow Registry[43] that functions interchangeably with others throughout the world including in the United Kingdom, Europe[159] and the American National Marrow Donor Program.[160] Logically such a network can provide an impartial repository to monitor country-wide activity with the further attraction of a database upon which to plan national protocols, co-operative clinical trials and research studies.

Conclusion

These procedures carried out in a properly constituted and dedicated unit continues to generate results that are comparable to those from established first world reference centers. The low transplant related mortality, rejection rate and graft-versus-host disease, previously reported are confirmed. The benefits of what is clearly a center effect cannot necessarily be extrapolated to similar interventions performed outside designated and monitored academically orientated facilities. In Third World countries, given current parlous financial climate and rampant retroviral epidemics, allocation of restricted resources for this purpose is rationally most sensible when limited to established, audited and accredited teams. Such a stance rests heavily on publication of outcome to justify ongoing support. It will also direct focus to actual achievement in contrast to the currently favoured incentive-driven preferred providers.

Acknowledgments

We recognise the courage of our patients and their families. Thanks to the staff in the Jeanne Porter apheresis and Bone Marrow transplant units, the Sunflower Haematology ward and the outpatient clinic for their high level of professionalism and care.

Supported by the Haematological Research and Education Trust and Chairman's Fund of the Anglo-American Corporation with grants from The Anthony Taberer, Louis Shill and Margaret Ward Foundations (Lucille Wood and Peter Jacobs): Manufacture of the Campath antibodies was supported by the UK Medical Research Council, the EP Abrahams Trust, Millennium Pharmaceuticals Inc (formerly LeukoSite Inc) and TolerRx Inc. Thanks are due to all members of the team at the Therapeutic Antibody Centre Oxford, notably Pru Bird, Patrick Harrison, Eleanor Berrie, Emma Bolam and Tony Gallagher. Tissue typing was via the South Africa Bone Marrow Registry and we recognise the excellence of that internationally accredited immunogenetics group.

Some of the work referred to in this thesis was an Honours project for BSc in Actuarial Science awarded to Jonathan Haveman.

We thank Mr Pedro Abrunhosa for help with the graphics. Christine Dölling for the bibliographic review and Natasha Trueman typed the manuscript: we record appreciation and thanks to our research staff.

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